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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

PAPER NO.: 24

Examiner:	Hope Robinson	
Art Unit:	1653	
Application	Serial Number:	09/339,352
	Filing Date:	June 23, 1999
	Appellant(s):	Berenice Y. Reed-Gitomer
		Charles Y.C. Pak

Mark B. Wilson

For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed on March 28, 2002.

EXAMINER'S ANSWER

(1) Real Party in Interest

This is in response to appellant's brief on appeal filed March 28, 2002. A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statements of the status of amendments after final rejection contained in the brief is correct. Additionally, a proposed claim was drafted for the appellant to obviate the present grounds of rejection and bring the application in condition for allowance, however, this proposed claim was declined by appellant (see the interview summary (Paper No. 23) and attached proposed claim).

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct as the rejection under 35 U.S.C. 112, second paragraph is withdrawn. The changes are as follows:

Whether claims 1-7, 10-15 and 17 lack utility under 35 U.S.C. 101.

Whether claims 1-7, 10-15 and 17 lack enablement under 35 U.S.C. 112, first paragraph.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1 and 2 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

Claim 12 has not been presented correctly. Accordingly, claim 12 is correctly written in the Appendix to the examiner's answer.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7, 10-15 and 17 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility based on screening for increased risk of developing hypercalciuria in a single subject by testing for any mutation(s) at/in chromosome 1q23.3-1q24. The present application on page 5, refers to the invention as "relating to the discovery that there exists an area on human chromosome 1 that is genetically linked to absorptive hypercalciuria (AH), and thus to some forms of osteoporosis. However, no discussion is provided as to where a mutation found in an individual subject demonstrates an increased risk for AH or what specific mutation must be detected to predict an increased risk of AH. The disclosure simply states that the present invention involves a simple, straightforward genetic test that can be implemented in diagnosing AH and osteoporosis with hypercalciuria in an individual subject (see page 6), which indicates the gene involved in AH would need to be identified by refining the locus.

Additionally, the specification does not clearly set forth how a standardized screening method would be developed to screen for increased risk of AH in an individual subject. Appellant discloses that the genomic region associated with an increased risk of AH may localize to more than one gene in this area, and that it is expected that there are several unique mutations associated with an increased risk of AH in different individuals (see page 123). This variability goes against the specification assertion that the invention provides a simple genetic test for increased risk of AH in an individual (see page 6). At page 2, line 28, appellants state that clinical and experimental data indicate that AH is heterogeneous in origin. Additionally, at page 3, line

21, appellants point out that strong evidence suggests involvement of a genetic process in AH, in that a familial pattern is present in 45% of reported cases, and an autosomal dominant inheritance pattern has been disclosed in the prior art. The specification at page 123, line 19, asserts that AH is inherited in an autosomal dominant mode due to a gene mutation in the chromosome 1q23.3-1q24 locus and that no genes of known function have been identified in this candidate region. At page 7, line 10, the specification teaches that a putative AH-genetically associated gene (SEQ ID NO: 1) has been identified by appellants, but this gene lacks portions of exon 1 and promoter sequences for transcriptional control for its expression (see page 128, paragraph 2). None-the-less, appellants were able to discern a mutation in the 5' non-translated region at C823A of SEQ ID NO: 1 in patients and these patients were heterozygous for this mutation, an expected finding for dominant mode inheritance (see page 129, paragraph 2). Therefore, the amino acid sequence of the encoded protein will not be affected by the C823A mutation but may affect stability or half-life of mRNA and the resulting amount of translated protein. RFLP analysis demonstrated that the C823A mutation is present in normal, AH and idiopathic osteoporotic populations (see Table 7, page 130) with a significantly higher occurrence in AH and idiopathic osteoporotic populations.

A second mutation was observed at T483C of SEQ ID NO: 1, 2 and a third and fourth in exon 2 but no tests were performed to demonstrate that these mutations were more than just polymorphisms (see page 130, paragraph 1). From the data presented, it is clear that the discovery of any mutation in chromosome 1q23.3-1q24 in an individual subject cannot indicate an increased risk of AH because mutations such as C823A of SEQ ID NO: 1 are found across

normal, AH and idiopathic osteoporotic populations and therefore no specific mutation has been shown to result in AH such that having the mutation indicates an increased risk of AH. As noted by appellants, AH is a familial disease and unique mutations associated with AH may occur in a dominant inheritance pattern. Therefore, the presence of a single mutation in an individual subject without comparison or an appropriate affirmed AH group is meaningless. The examples (1-7) do not demonstrate nor describe the claimed method of screening for increased risk of AH in an individual subject with all possible genetic mutation.

The assertion that a gene mutation in the chromosome 1q23.3-1q24 is responsible for AH on page 123 of the specification and statement made of a simple genetic test to screen for an increased risk of AH followed by a discussion of the uncertainty of the gene region genes and variability of the mutation, may be indicia of a "real world" context of use. See for instance, Example 5, which states that the example describes a putative gene located in the region and the relationship between this putative gene and AH. The example also states that "should the putative gene described in this example eventually be shown not to be the AH gene, similar methodologies as described throughout the specification and proceeding examples will be used to identify the true AH gene (see pages 127-128) which highlights the uncertainty. Therefore, because applicant has not disclosed any specific or substantial utility for the claimed invention, credibility will not be assessed.

Claims 1-7, 10-15 and 17 also stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

(11) Response to Argument

A. Claim 1 has an Asserted Utility

This section of the appeal brief is not an argument, but a summary as appellants summarize their invention.

On page 6 of the appeal brief appellants state that an invention has utility if a particular purpose is asserted in the specification and a person of ordinary skill would consider this assertion credible. Specifically, at page 6, paragraph 2, appellants state that the specification utility is the use of the claimed genomic locus in screening for an increased risk of developing hypercalciuria because the specification sets forth a genetic locus that is statistically related to the AH phenotype in the screened kindred groups. The Examiner agrees. However, the claims as written are drawn to screening individuals for mutations in the claimed genomic locus without screening kindred groups, for example. The specification does not provide a specific mutation that can routinely be asserted to be indicative of an increased risk of AH. Rather, for example, C823A mutation in SEQ ID NO: 1 can also indicate idiopathic osteoporosis or nothing at all. This

observation, combined with appellants notations that unique mutations may exist per kindred group having AH supports the Examiner's view that the claims as written lack utility.

It is noted that on pages 129-130 the specification states that probands from 2 of the kindred's examined revealed the same point mutation of C to A transversion mutation in SEQ ID NO: 1. It is stated that this could lead to either an increased amount or decreased amount of the encoded protein, resulting in the AH phenotype using putative gene (exon 5). Thus, the specification implies but does not demonstrate that an increased or decreased amount of the encoded protein leads to an AH phenotype. The specification further states that analysis of AH patients led to the identification of a second mutation a T to C transition mutation (exon 4). Additionally, the specification states that analysis of 91 AH patients with this method identified 13 patients with two distinct mutations in exon 2 of the putative gene. It is stated that with each new mutation, sequence analysis will be performed to ensure that the new mutations found are not simply polymorphism. However, the specification does not indicate that this occurred or that the mutations were not simply polymorphisms. Note also that claim 1 as written is inoperable, thus has no utility. The claim has no comparison group and one of skill in the art would not be able to ascertain if screening is occurring in patients with mutations, having an allele for the disease or patients with the same mutation with no allele for the disease. Additionally, the specification does not teach where the mutation demonstrates an increased risk for AH or provide any patient data to demonstrate that any mutation results in an increased risk for AH, including deletion of the

genomic region. The following claim was drafted to obviate the present grounds of rejection, however was declined by the appellant:

"A method for screening for an increased risk of hypercalciuria in a subject comprising:

(a) determining mutations that indicate an increased risk of hypercalciuria by:

(i) screening a group of subjects having confirmed hypercalciuria for mutations in the genomic region comprising chromosome 1q23.3-1q24, wherein said screening method comprises obtaining a nucleic acid sample from each subject and detecting mutations in said genomic region;

(ii) screening a group of control subjects for mutations in the genomic region comprising chromosome 1q23.3-1q24, wherein said screening method comprises obtaining a nucleic acid sample from each subject and detecting mutations in said genomic region;

(iii) determining mutations that indicate an increased risk of hypercalciuria by comparing the presence of genetic mutations in said genomic region of the group of subjects having confirmed hypercalciuria with the genetic mutations in said genomic region of the group of control subjects, wherein the presence or preponderance of mutations found in the group of subjects having confirmed hypercalciuria and not found or found to a lesser extent in the group of control subjects indicates a mutation that is associated with increased risk of hypercalciuria;

(b) obtaining a sample nucleic acid from an individual subject;

(c) analyzing the sample nucleic acid from said individual subject to detect the presence or absence of a genetic mutation in the genomic region comprising chromosome 1q23.3-1q24, and

(d) comparing the presence of a genetic mutation in the genomic region comprising chromosome 1q23.3-1q24 of said individual subject determined in step (a)(iii), wherein the presence of a mutation in the individual subject that corresponds to mutation determined in step (a)(iii) is indicative of increased risk of hypercalciuria in said individual subject".

At paragraph two on page 6, the appellants state that a person of ordinary skill will recognize that the instant invention provides substantive evidence that localizes a disease susceptibility phenotype to a specific genetic locus. It is also stated that localization of mutations in a genetic locus requires the practice of simple screening processes, such screening process are well-known to those of skill in the art and described in the specification. However, the amount of variability that can occur based on the types of mutations to the genomic region goes against the appellant's assertion that the specification provides a simply screening process (see page 123 where it is stated that several unique mutations are associated with an increased risk of AH in different individuals). Further, a possible mutation can be deletion of the entire region the appellant calls the genomic region. How then does deletion lead to an AH phenotype?

On page 7, appellants state that the instant invention provides substantive evidence that localize AH phenotype to a specific genetic locus. Again, the Examiner agrees. However, simply having a mutation in the claimed genetic locus means nothing without comparison of mutations found in appropriate groups having AH. The appellants point to examples 3-5, with specific emphasis on example 5. Note that Example 5, states that the example describes a putative gene

located in the region and the relationship between this putative gene and AH. The example also states that "should the putative gene described in this example eventually be shown not to be the AH gene, similar methodologies as described throughout the specification and proceeding examples will be used to identify the true AH gene (see pages 127-128). The unpredictability of the claimed invention is again emphasized.

The Declaration of Drs. Pak and Reed-Gitomer filed under 37 CFR 1.132 filed March 28, 2002 (Paper No. 18) and the discussion of this Declaration on pages 8-11 is insufficient because at the time the application was filed, none of the additional data presented in the Declaration were known, and such is not disclosed in the specification so that one skilled in the art can use the teachings of the resulting patent(s) and practice the claimed invention. The appellants urge that the new data provided reveals six base changes in the 1q23.3-1q24 region, of which four were shown to indicate a significant increase in the relative risk for AH. The appellants also state that in view of the new data the invention does not lack utility... and the occurrence of mutations in the 1q23.3-1q24 region are linked to an increased risk of hypercalciuria... (this correlation does not appear limited to a single or small subset of mutations,... in fact, most such mutations thus far have been found to be indicative in a significantly increased risk of AH). However, no prediction can be made as to which mutation will lead to an increased risk of AH from the data submitted.

At page nine, paragraph two, the appellants urge that it would not require undue experimentation to perform similar screening on individuals at risk for AH using methods similar to those set in the specification but restricted to the claimed loci. It is further stated that a person

of ordinary skill would be aware of more refined methods to screen for chromosomal deletions, alterations or other mutations. The specification highlights the variability that can occur in terms of the type of mutations within the genomic region which is exemplified in the newly submitted declaration. In addition, the appellant's statement that a skilled artisan would be aware of more refined methods to screen for chromosomal deletions, alterations etc., is an acknowledgment that deletions not just the point mutation referred to in example 5 can occur, which raises the issue of whether a single residue will be deleted or the entire region. Additionally, the specification and the declaration state that the mutations can vary and that not all the mutations found led to an increased risk of AH. Therefore, undue experimentation is required to practice the claimed invention with the vast variability of mutation encompassed, the unpredictability and the fact that all mutations that occur in that region is not associated with an increased risk.

At page 10, the appellants urge that it is examiner's mere contention that undue experimentation due to the absence of data is merely speculation. Indeed not; to practice the claimed invention one would have to have provided the specific mutations that will be indicative of AH as noted above. The specification does not set forth how a standardized screening method would be developed to screen for an increased risk of AH and it is stated that the genomic region associated with an increased risk of AH may localize to more than one gene in this area and it is expected that there are several unique mutations associated with an increased risk of AH. Thus, undue experimentation is required to determine which mutation is associated with an increase in AH, as demonstrated in the data presented in the declaration post-filing. Therefore, the burden of

proof has been met. The Courts stated in *In re Gardner (166 USPQ 138)* that: the law requires that disclosure in an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. The situation at hand is analogous to that in *Genetech v. Novo Nordisk A/S 42 USPQ2d 1001.* As set forth in the decision of the Court: "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (FED. Cir. 1993)*; see also *Amgen Inc. v. Chugai Pharms. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016 (Fed Cir. 1991); In re Fisher, 427 F.2d 833, 166 USPQ 18, 24 (CCPA 1970)* ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See *Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)* (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.'). Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. "It is true...that a specification need not disclose what is well known in the art. See, e.g., *Hybritech, Inc. v. Monoclonal*

Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research (emphasis added).

B. Claim 1 is Enabled

The argument at page 11, paragraph 3 has been discussed above. Appellants discuss their claimed invention from pages 11-13. Page 11, paragraph four, states that "a rejection based on lack of enablement must be adequately supported by substantive evidence....The PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has acceptable evidence or reasoning to suggest otherwise... The PTO must...provide reasons supported by the record as a whole of what the specification is not enabling....Then and only then does the burden shift to the applicant to show that one of ordinary skill in the art could have practiced the claimed invention without undue experimentation....The action has erroneously

placed the burden of proof on the appellants without offering any evidence or reasoning based on the record as a whole why the disclosure is not enabling for the pending claim". The appellant's statements are incorrect as the rejection made under 35 U.S.C. 112, first paragraph, enablement, was made specifically, since the claimed invention is not supported by either an asserted utility or a well established utility for the reasons set forth above which is stated on the record. At page 13, paragraph 1, appellants state that they do not appreciated the assertion that the Example 5 is inadequate to establish enablement. Example 5 has been addressed above. The Example refers to point mutations, however, the disclosure acknowledges other types of mutations, for example, deletions can occur not just the point mutation referred to in example 5, which raises the issue of whether a single residue will be deleted or the entire genomic region.

C. Claim 1 is Definite

Note that this rejection has been withdrawn.

E. The Application Should Receive the Provisional Filing Date

The appellant's brief presents arguments relating to the claim for priority. This issue is not an appealable subject matter.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Examiner Hope Robinson

May 22, 2002

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APPENDIX- PRESENTATION OF CLAIM 12

12. The method of claim 1, wherein the genomic region has a sequence contained in at least one genetic sequence selected from the group consisting of the genetic sequences set forth in GenBank Accession # Z97876 (SEQ ID NO: &, SEQ ID NO: 8 and SEQ ID NO: 9), GenBank Accession # Z99943 (SEQ ID NO: 10), and GenBank Accession # AL031733 (SEQ ID NO: 7).